ELSEVIER
Journal of Cystic Fibrosis 2 (2003) 25–28
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

# A pilot study of zafirlukast as an anti-inflammatory agent in the treatment of adults with cystic fibrosis

S.P. Conway[a,*], C. Etherington[a], D.G. Peckham[a], A. Whitehead[b]

[a]*Regional Adult CF Unit, Seacroft Hospital, York Road, Leeds, UK*
[b]*Pharmacy Department, Seacroft Hospital, York Road, Leeds, UK*

**Abstract**

*Background*: Persistent endobronchial inflammation is in part responsible for the attrition of lung function seen in cystic fibrosis. Leukotrienes act as pro-inflammatory mediators. The aim of this study was to assess the efficacy of the leukotriene receptor antagonist zafirlukast as a potential anti-inflammatory agent in the treatment of adult patients with cystic fibrosis. *Methods*: Clinically stable patients were enrolled in the study if they had no history or clinical evidence of asthma, bronchial hyper-reactivity, or aspergillosis. They were randomised to receive zafirlukast 20 mg twice daily with all routine treatment for four months or routine treatment alone in an open cross-over design. Primary endpoints were changes in respiratory function tests and a modified NIH clinical score. *Results*: Thirty patients were enrolled and 25 completed. There was a significant improvement in the modified NIH clinical score but no significant increase in respiratory function with zafirlukast. *Conclusions*: Patients receiving a leukotriene receptor antagonist in addition to routine treatments showed significant improvement in a clinical score which is a composite of clinical wellbeing, chest radiograph appearance, and physical examination. Respiratory function showed a non-significant trend towards improvement with treatment. Zafirlukast may benefit patients with CF. An adequately powered study is justified on the basis of these results.


*Keywords:* Cystic fibrosis; Leukotriene receptor antagonists; Anti-inflammatory

## 1. Introduction

Leukotrienes (LTs) are formed from activated inflammatory cells. These proinflammatory chemical mediators recruit other inflammatory cells to lung tissue and in the airways stimulate mucus hypersecretion, oedema and bronchospasm [1]. The C4, D4, and E4 LTs, referred to as the cysteinyl-LTs as each has a thio-ether linked peptide, all use the $CysLT_1$ airway receptor site. Zafirlukast acts as a LT receptor antagonist, interrupting the inflammatory cascade by preventing the cysteinyl-LTs activating the receptor. Randomised, double-blind, placebo-controlled trials have shown significant improvements in asthma symptoms and lung function following treatment with zafirlukast 20 mg twice daily [2,3].

The important negative effect of uncontrolled inflammation on lung function in cystic fibrosis (CF) is well documented [4,5]. The pathogenic potential of LTs in CF has been suggested by several studies. Sampson et al. [6] showed that children with CF had greater urinary LTE4 levels than controls. Urine levels correlated significantly with sputum LTE4 levels and with the total cysteinyl-LT content in sputum. High levels of both LTE4 and LTB4 were found in sputum. Spencer et al. [7] documented high sputum cysteinyl-LT levels, which correlated with the overall severity of the pulmonary disease in children. Greally et al. [8] showed a significant positive correlation between TNF-alpha and both LTB4 and total cysteinyl-LT sputum content. Respiratory function was inversely related to TNF-alpha concentrations, suggesting that both LTs and TNF-alpha may be involved in airway inflammation and obstruction in CF. These studies suggest a role for LTs in the pathophysiology of CF.

There are only two studies on the use of LT receptor antagonists in CF. Morice et al. [9] gave montelukast to 11 stable but otherwise unselected patients with CF for 2 weeks in an open label trial. Patients documented subjective improvement and better exercise tolerance. Schmitt-Grohe et al. [10] gave montelukast or placebo to 16 patients with CF for 21 days each in a cross-over

*Corresponding author.

1569-1993/03/$30.00 
doi:10.1016/S1569-1993(02)00142-X

Table 1
Mean values (S.D.) of baseline assessments for primary outcome variables

| | Number | FEV1(l) | FEV1 (%pred) | FVC(l) | FVC (%pred) | $FEF_{25-75}$(l) | $FEF_{25-75}$ (%pred) | Modified NIH score (0–50) |
|---|---|---|---|---|---|---|---|---|
| Group 1 Zafirlukast Period 1 | 11 | 2.25 (1.03) | 59 (20.8) | 3.3 (1.2) | 75.5 (20.6) | 1.47 (0.99) | 31.1 (18.8) | 20.5 (7.4) |
| Group 2 Zafirlukast Period 2 | 14 | 2.45 (1.01) | 64.4 (24.4) | 3.54 (0.93) | 79.9 (19.4) | 1.99 (1.87) | 43.9 (38.6) | 18.8 (6.7) |

study. They found a significant reduction in serum eosinophilic cationic protein and in eosinophils, suggesting that blocking of the LT receptor might reduce eosinophilic inflammation.

The aim of this study was to see if the anti-inflammatory effects of zafirlukast resulted in improvements in lung function and clinical wellbeing in adult patients with CF who had no evidence of bronchial hyperreactivity or allergic bronchopulmonary aspergillosis (ABPA).

## 2. Patients and methods

Clinically stable patients were invited to participate in the study. Exclusion criteria were any of the following; history of recent ABPA or asthma, bronchodilator reversibility $>15\%$, raised peripheral blood eosinophil count, serum IgE $>200$ IU, or positive aspergillus RAST or precipitin test results. Patients were randomised to receive zafirlukast 20 mg twice daily plus all routine treatments for 4 months followed by routine treatment alone for 4 months, or vice versa, in an open-label cross-over trial. A washout period was not introduced between the two arms of the study as only data from the end of each treatment period were analysed, except for days of additional antibiotic therapy (a secondary outcome variable).

Patients received the following concomitant respiratory directed therapies; nebulised antibiotics 55%, bronchodilators 93%, oral corticosteroids 21%, inhaled corticosteroids 66%, pulmozyme 52%.

Outcome measures were recorded at baseline and at 2 monthly intervals to 8 months. These included respiratory function tests (RFTs), weight, and peripheral blood inflammatory markers (c reactive protein, white cell count, IgG, plasma viscosity). Four clinical scores were completed, modified from Ranasinha et al. [11] Dyspnoea was represented by a 100 mm vertical line ranging from no shortness of breath at the bottom to severe shortness of breath at the top [12]. Patients scored the line according to perceived dyspnoea experienced. Answers to questions on general well being (feeling, energy, physical activity, appetite and sleep pattern) and on CF related symptoms (ease of sputum expectoration, cough frequency and severity, congestion, wheeze) were ranked on a 5-point Likert scale in which one represented the worst symptoms and five represented no symptoms. Finally a modified NIH score (details available on request) was used to assess overall clinical status [13] at 0, 4 and 8 months. At each visit patients were asked to report the number of days on which additional oral or intravenous antibiotics had been prescribed.

Primary outcome measures were changes in RFTs, absolute values and percent predicted, and the modified NIH clinical score. The data were analysed according to the methods of Hills and Armitage for cross-over studies [14]. *T*-tests were applied to test for treatment by period interactions, period effects and treatment effects. For all variables except days of additional antibiotic therapy the data recorded at 4 and 8 months were used in the analysis as the assessments of response in the first and

Table 2
Mean values (S.D.) of baseline assessment for secondary outcome variables

| | Number | Weight (kg) | Crp (mg/l) | Plasma viscosity (cP) | White cell count ($\times 10^9$/l) | IgG (g/l) | Dyspnoea score (mm) | General wellbeing score (0–25) | CF symptom score (0–25) |
|---|---|---|---|---|---|---|---|---|---|
| Group 1 Zafirlukast Period 1 | 11 | 60 (10.5) | 12.6 (6.6) | 1.81 (0.09) | 12.1 (4.9) | 14.8 (3.7) | 23.4 (16.5) | 20 (4.3) | 17.5 (3.4) |
| Group 2 Zafirlukast Period 2 | 14 | 60.8 (8.9) | 14.3 (14.8) | 1.8 (0.19) | 10.2 (2.9) | 13.9 (3.4) | 13.8 (13.1) | 22.6 (3) | 20.5 (2.1) |

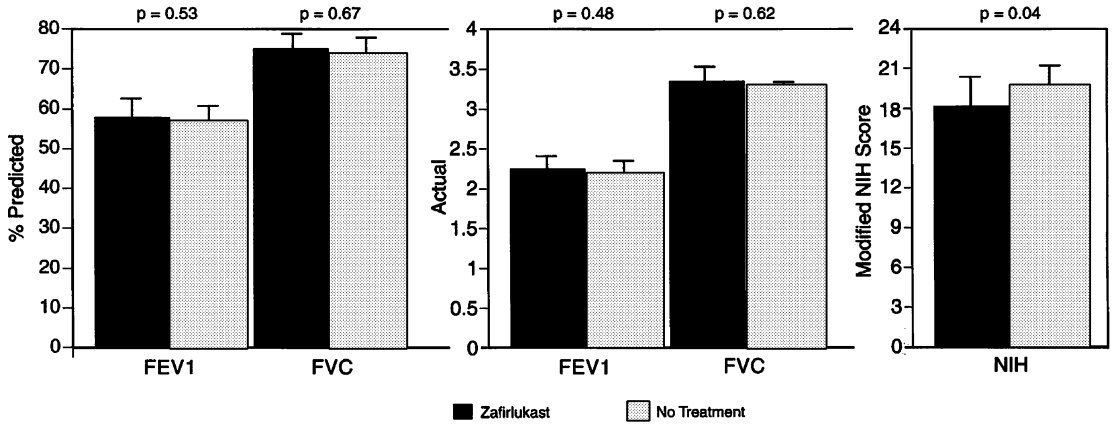


Fig. 1. Mean responses (S.E.) in each treatment arm for primary outcome variables.

second treatment periods respectively. For days of added intravenous and oral antibiotic therapy, responses during the first and second periods were denoted respectively, by the sum of the data recorded at 2 and 4 months, and at 6 and 8 months. In all tests a $P$-value $<0.05$ denoted statistical significance.

## 3. Results

Thirty patients, (15 male), were entered into the study. Mean patient age was 24 years (range 20–32 years). Due to the cross-over design all patients were required to have had at least one assessment of efficacy for both treatment periods to be eligible for analysis. Consequently five patients (two receiving zafirlukast in the first period) were excluded as they withdrew before the start of the second treatment period. The withdrawals were not related to any adverse event or drug side effect. Eleven of the remaining 25 received zafirlukast in the first treatment period.

The baseline data are summarised in Tables 1 and 2. Mean responses for primary outcome variables are shown in Fig. 1. Mean responses and treatment effects for secondary outcome variables are shown in Table 3. There was no evidence of a significant treatment by period interaction for any variable and therefore the cross-over methods could be applied to all variables.

With respect to the primary variables, the modified NIH score was significantly lower on zafirlukast compared to routine treatment, (estimated treatment effect $-1.57$, $P<0.05$). Both absolute and percent predicted values for FEV1 and FVC were non-significantly higher on zafirlukast, (effect size 0.04 l, 0.81% and 0.04 l, 0.91%, respectively). $FEF_{25-75\%}$ values showed a significant period effect ($P=0.01$) and tended to be higher in the first treatment period irrespective of which treatment the patient was receiving. Consequently the estimates of the treatment effects for $FEF_{25-75\%}$ are not reliable as it is impossible to separate out the true treatment effect from the period effect.

With respect to the secondary outcome measures there was no evidence of a significant difference between zafirlukast and routine treatment for any of the variables. Significant period effects were apparent for c-reactive

Table 3
Mean responses (S.D.) and treatment effects in each treatment arm for secondary outcome variables

| | Number | Wt. (kg) | Intra-venous anti-biotics (days) | Oral anti-biotics (days) | CRP (mg/l) | Plasma viscosity (cP) | White cell count ($\times 10^9$/l) | IgG (g/l) | Dyspnoe score (mm) | General well-being score (0–25) | CF symptom score (0–25) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean responses | | | | | | | | | | | |
| Zafirlukast | 25 | 60.8 (9.5) | 12.8 (12.9) | 6.9 (8.9) | 14.4 (16.8) | 1.78 (0.14) | 10.5 (4.2) | 13.8 (3.6) | 18.8 (19.5) | 21.6 (2.8) | 19.3 (3.2) |
| No treatment | 25 | 61 (9.6) | 12.4 (15.1) | 5 (8.3) | 15.4 (15.8) | 1.81 (0.16) | 9.5 (3.4) | 14.3 (3.3) | 25.3 (24.8) | 20.6 (4.4) | 17.9 (4.1) |
| Treatment effect | | | | | | | | | | | |
| Effect size | | 0.14 | −0.19 | 1.27 | −2.01 | −0.03 | 0.73 | −0.55 | −6.62 | 0.99 | 1.32 |
| 95% CI | | 0.9 0.62 | −6.44 6.07 | −2.08 4.61 | −9.74 5.71 | −0.08 0.02 | −1.21 2.66 | −1.17 0.07 | −14.9 1.67 | −0.98 2.95 | −0.43 |
| $P$ value | | 0.69 | 0.95 | 0.4 | 0.6 | 0.26 | 0.44 | 0.08 | 0.11 | 0.3 | 0.13 |

protein ($P=0.04$) and total peripheral blood white cell count ($P=0.02$), with both variables tending to be lower in period one. The treatment effects associated with them should therefore be interpreted with caution.

No adverse events were reported.

## 4. Discussion

In adult patients with CF, who were selected to minimise any benefits that might be derived from its efficacy as an asthma drug, the addition of the LT receptor antagonist zafirlukast to routine treatment regimens significantly improved patients' clinical status as measured by a modified NIH score. There were non-significant improvements in respiratory function, plasma viscosity, IgG levels, dyspnoea, wellbeing and CF symptom scores, and fewer days of intravenous therapy. Twenty-five patients completed the trial and greater differences between treatment with and without zafirlukast may be evident in a larger multicentre study.

Morice et al. [9] attributed the efficacy of a LT receptor antagonist in CF to a blockage of the effects of *Aspergillus* stimulated Th2 inflammation and LT synthesis. In our study we excluded patients with evidence of immunological reactivity to *Aspergillus* infection as well as those with significant bronchial reversibility. We suggest that any benefit from the LT receptor antagonists in clinically stable patients with CF is a reflection of their interference with the persistent lower respiratory tract inflammation that characterises this disease. This hypothesis is supported by Schmitt-Grohe et al. who presented data at the 24th European CF Conference 2001 which showed a montelukast induced fall in eosinophilic inflammation [10].

LTB4 may be important in mediating neutrophil influx and activation, hence encouraging the neutrophil dominated inflammation in the CF lung [15,16]. Zafirlukast does not block the LTB4 receptor. Treatment that interferes with the action of LTB4 as well as the cysteinyl-LTs, for example 5-lipoxygenase inhibitors that block LT production from eicosanoids, might further benefit patients.

Our data suggest that treatment with zafirlukast may benefit patients when they are assessed by a clinical score which includes chest radiograph appearance, physical examination, presence or not of haemoptysis, sputum characteristics, and general health measures such as appetite, energy, exercise tolerance and dyspnoea. Plasma viscosity, serum IgG, and a dyspnoea score were also lower with treatment, and respiratory function, general well-being and CF symptom scores better. When receiving zafirlukast patients needed less days of intravenous antibiotic therapy. However, the differences between treatments only reached statistical significance for the modified NIH clinical score.

In conclusion, we have shown that the LT receptor antagonist, zafirlukast, results in a measurable clinical improvement in adult patients with CF and appears to be well tolerated. We suggest that there is now sufficient data to warrant evaluation of the role of LT antagonists in CF in an adequately powered clinical trial.

## References

[1] Chanarin N, Johnston SL. Leukotrienes as a targeted asthma therapy. Drugs 1994;47:12–24.
[2] Fish JE, Kemp JP, Lockey RF, Glass M, Hanby LA, Bonuccelli CM. Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicentre study. Clin Ther 1997;19:675–90.
[3] Nathan RA, Bernstein JA, Bielory L, Bonuccelli CM, Calhoun WT, Galant SP, Hanby LA, Kemp JP, Kylstra JW, Nayak AS, O'Connor JP, Schwartz HJ, Southern DL, Spechors SL, William PV. Zafirulast improves asthma symptoms and quality of life in patients with moderate reversible air flow obstruction. J Allergy Clin Immunol 1998;102:935–42.
[4] Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and aetiology. Pediatr Pulmonol 1997;24:137–42.
[5] Berger M, Konstan MW. Immunopathogenesis of cystic fibrosis lung disease. In: Yankaskas JR, Knowles MR, editors. Cystic Fibrosis in Adults. Lippincott-Raven, 1999. p. 115–43.
[6] Sampson AP, Spencer DA, Green CP, Piper PJ, Price JF. Leukotrienes in the sputum and urine of cystic fibrosis children. Br J Clin Pharmacol 1990;30:861–9.
[7] Spencer DA, Sampson AP, Green CP, Costello JF, Piper PJ, Price JF. Sputum cysteinyl–leukotriene levels correlate with the severity of pulmonary disease in children with cystic fibrosis. Pediatr Pulmonol 1992;12:90–4.
[8] Greally P, Hussein MJ, Cook AJ, Samson AP, Piper PJ, Price JF. Sputum tumour necrosis factor-alpha and leukotriene concentrations in cystic fibrosis. Arch Dis Child 1993;68:389–92.
[9] Morice AH, Kastelik JA, Aziz I. Montelukast sodium in cystic fibrosis. Thorax 2001;56:244.
[10] Schmitt-Grohe S, Eickmeier O, Bez C, Schubert R, Steffan J, Zielen S. Randomised controlled trial of montelukast (Singulair) in cystic fibrosis. J Cystic Fibrosis (2001), Abstracts of 24th European Cystic Fibrosis Conference, Vienna, poster 167.
[11] Ranasinha C, Assoufi B, Shak S, et al. Efficacy and safety of short-term administration of aerosolised recombinant human DNase1 in adults with stable stage cystic fibrosis. Lancet 1993;342:199–202.
[12] Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnoea. Rehab Nurs 1989;14:323–5.
[13] Taussig LM, Kattwinkel J, Friedewald WT, di Sant Agnase PA. A new prognostic score and clinical evaluation system for cystic fibrosis. J Pediatr 1973;82:380–90.
[14] Hills M, Armitage P. The two-period cross-over clinical trial. Br J Clin Pharmacol 1979;8:7–20.
[15] Lawrence R, Sorrell T. Eicosapentaenoic acid in cystic fibrosis: evidence of a pathogenetic role for leukotriene B4. Lancet 1993;342:465–9.
[16] Konstan MW, Walenga RW, Hilliard KA, Hilliard JB. Leukotriene B4 markedly elevated in the epithelial lining fluid of patients with cystic fibrosis. Am Rev Respir Dis 1993;148:896–901.